REMARKS

This Reply is responsive to the Office Action dated January 16, 2002. Original claims 2-90 are canceled and new claims 91-120 are submitted. Entry of the foregoing and reconsideration on the merits pursuant to 37 CFR 1.112 is respectfully requested.

Amendment of the Text of the Specification:

The specification has been amended as set forth above. In accordance for the new rules for amending applications set forth in 37 CFR 1.121, which took effect on March 1, 2001, a marked up version of the text of each amended paragraph, showing the changes that were made, is attached hereto as an appendix.

A. Amendment of the Brief Description of the Drawings

The specification was objected to because each drawing must be separately described. The Brief Description of the Drawings is amended so that each drawing is separately described.

B. Additional Amendment of the Specification – Related Applications

The first paragraph on page 1 of the specification is amended to correct and update the cross-references to related applications.

The above-described amendments do not add new matter to the application.

Support for the New Claims in the Specification and in the Original Claims:

New independent claims 91 and 106 both recite a composition comprising transgenic totipotent ungulate CICM cells of a CICM cell line that express a transgene, and also comprising cells of the same CICM cell line that do not express the transgene. New claims 91-105 are directed to the claimed composition in which the CICM cells are a line of bovine CICM cells; and new claims 106-120 recite a similar composition in which the CICM cells are porcine CICM cells. The claimed composition is produced, for example, when a heterologous DNA expression construct is introduced into cells of a CICM cell line, and a fraction of cells in the composition in which the construct is expressed is selected. Totipotent cells are able to give rise to germ cells, from which are derived every cell type in the body. Applicants contend that in the mid-'90s, when the application was filed, little was known about the conditions required to preserve the totipotency of cultured CICM cells, and that until the Applicants actually demonstrated the operability of the invention, it would have been impossible to predict whether a stable culture (i.e., a cell line) of CICM cells, either bovine or porcine, could be genetically modified in culture without loss of totipotency.

Support for the new claims is found in original claim 82, which recited a stable culture comprising transgenic bovine CICMs; and also at page 41, lines 1-13, which describes a composition of CICM cells comprising both expressing transgenic CICM cells and non-expressing CICM cells, and in Example 5 (pages 43-45), which describes generating bovine and porcine germ-line chimeras with transgenic CICMs.

Description of heterologous DNA constructs that can be introduced into CICMs according to the invention is found at page 39, and description of constructs encoding selectable markers and their use to identify expressing transgenic cells is found, for example, at pages 30 and 40-41. Description of transfecting CICM cells with constructs encoding DI genes is found, for example, at the top of page 17, and in the paragraph bridging pages 31-32.

Constitutive promoters such as those recited in claim 98 are described in the paragraph bridging pages 38-39; and description of inducible promoters such as those recited in claims 99 and 100 is found, for example, at the top of page 32, and the bottom of page 42. Support for the properties of CICMs as recited in claims 101 and 102 is found in original claims 85 and 86; and a cell composition comprising a feeder layer as recited in claims 103-105 is found in original claims 88-90.

No new matter has been introduced by the amendment.

Rejections of claims under 35 U.S.C. §112, second paragraph:

Claims 82, 83, and 89 were rejected under 35 U.S.C. §112, second paragraph as being indefinite. The recitation of "comprising transgenic bovine CICMs" in original claim 82 was regarded as being indefinite because it was unclear whether the culture included both transgenic and non-transgenic CICM cells. This issue has been addressed in the new claims, by reciting that the composition of CICM cells comprises transgenic bovine CICM cells of a CICM cell line that express a transgene, and also comprises cells of the CICM cell line that do not express the transgene. The methods for introducing genetic constructs into cells described in the specification may result in transfecting some or all of the CICM cells of the composition; however, as described in the specification (page 41, from line 6), expression constructs are s often not expressed in many of the cells into which they are transfected. Accordingly, selection methods typically identify the cells that express a transgene, not the cells that contain but do not express the construct.

The objected-to term, "multilayer portion," in original claim 83 is not present in the new claims. With regard to the meaning of the language of claim 89, the new claims are drafted with the view that "a stable culture of CICM cells" is generally equivalent to "a CICM cell line," as observed by the Examiner in the Office Action (p. 4)

Rejection of the claims for double patenting:

The objection to claim 90 as being a substantial duplicate of claim 79 is moot, as these claims are cancelled .

Rejections of claims under 35 U.S.C. §102(b)

Claims 79-85 and 90 were rejected under 35 U.S.C. §102(b) as being anticipated by Sims et al. (PNAS, 1993), and also under 35 U.S.C. §102(e) as being anticipated by Sims et al. (US Patent No. 6,107,543). The teachings of the two Sims et al. references are similar.

Applicants acknowledge that Sims et al. disclose untransfected bovine CICM cells similar to those disclosed by the present application. However, while Sims et al. only suggest transferring transgenes into the cells (columns 13-14); they do not actually demonstrate that this can be done without loss of totipotency. In the mid-1990s, when the Sims et application was filed, no one had shown that ungulate isolated embryonic stem cells could be successfully genetically modified without loss of totipotency, and the phenotype of transfected ungulate embryonic stem cells was unpredictable. Isolated embryonic stem cells were generally recognized as being unstable, in that it was difficult to identify conditions under which they could be cultured without loss of totipotency or pluripotency. The manipulations associated with introducing heterologous DNA expression constructs into a cell were generally regarded as being likely to de-stabilize embryonic stem cells and cause them to lose their totipotency. The composition of CICM cells recited in the present claims was produced by applicants in carrying out their disclosed method for genetically modifying cultured bovine and porcine CICM cells are without loss of totipotency. Sims et al. does not disclose such a composition, and until the Applicants carried out the steps leading to the production of the claimed composition, it was impossible to predict whether and how it could be produced. Accordingly, reconsideration and withdrawal of the rejection under §102 (b) is respectfully requested.

Rejections of claims under 35 U.S.C. §103(a)

Claims 79-90 were rejected under 35 U.S.C. §103(a) as being unpatentable over Sims et al., Deboer et al., and Stewart et al.

As noted above, Sims et al. disclose the isolation of untransfected totipotent bovine CICM cells; however, although they suggest transferring transgenes into such cells, they do not show that this can be done without loss of totipotency. Deboer et al. disclose methods for generating a transgenic bovine by which transgenic CICM cells could be derived; and Stewart et al. disclose culturing CICM cells on a fibroblast feeder layer. While the combination of these references might lead one of ordinary skill in the art to obtain transgenic CICM cells from a transgenic bovine made according to Deboer et al., and to culture them on a fibroblast feeder layer according to Stewart et al., nothing in the cited references suggests the claimed composition, comprising transgenic totipotent bovine or porcine cells of a CICM cell line that express a transgene, and also comprising cells of the same CICM cell line that do not express the transgene, could be made with a reasonable expectation of success.

As discussed above, at the time the invention was made, no one had shown that ungulate isolated embryonic stem cells could be successfully genetically modified without loss of totipotency, and the phenotype of transfected ungulate embryonic stem cells was unpredictable. The phenotype of isolated, cultured embryonic stem cells was considered to be unstable, and the manipulations associated with introducing heterologous DNA expression constructs into such cells were regarded as being likely to de-stabilize them and cause them to lose their totipotency. The composition of CICM cells recited in the present claims is produced by the Applicants in carrying out their disclosed method for genetically modifying cultured bovine and porcine CICM cells are without loss of totipotency. None of the prior art references, alone or in combination, disclose or suggest making the claimed composition with a reasonable likelihood of success. Accordingly, reconsideration and withdrawal of the rejection under §103(a) is respectfully requested.

All of the issues raised by the Office Action dated December 19, 2001, have been addressed in this Reply. Accordingly, a Notice of Allowance is next in order. If the Examiner has any further questions or issues to raise regarding the subject application, it is respectfully requested that she contact the undersigned so that such issues may be addressed expeditiously.

Respectfully submitted,

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Date: May 20, 2002

APPENDIX

The following amendments were entered by way of the amended disclosure and claims presented for consideration above:

IN THE SPECIFICATION:

Please replace the paragraph beginning at line 7 of page 1, previously amended by the preliminary amendment filed November 8, 1999, with the following amended paragraph:

-- Related Applications

This application is a divisional of U.S. Application No. 08/766,939, filed December 16, 1996, now U.S. Patent No. 5,994,619, which in turn is a continuation-in-part of U.S. Application No. 08/626,054, filed April 1, 1996, now U.S. Patent No. 5,905,042. [This application is a continuation-in-part of co-pending U.S. application No. 08/626,054] --

Please replace all of the lines of the Brief Description of the Figures on page 14, from line 14 to the bottom of the page, with the amended text shown below:

- - BRIEF DESCRIPTION OF THE FIGURES

FIG. 1 is a photograph of cultured CICM cells grown without feeder layer contact. Embryoid bodies may be observed.

FIG. 2 is a photograph of cytokeratin positive cultured CICM cells.

FIG. 3 is a photograph of CICM cells on a fibroblast feeder layer. Multiple layer colonies are visible after only 2 days of culturing.

FIG[S]. 4 [and 5 are] is a photograph[s] showing AP positive and cytokeratin negative CICM cell colonies.

FIG. 5 is a second photograph showing AP positive and cytokeratin negative CICM cell colonies.

FIG[S]. 6 [and 7 are] is a photograph[s] showing epithelial-like cells which are obtained during culturing of CICM cells. Those cells are AP negative and cytokeratin positive.

FIG. 7 is a second photograph showing epithelial-like, AP negative and cytokeratin positive cells which are obtained during culturing of CICM cells.

FIG. 8 is a photograph of CICM cell colonies. This photo shows that multilayer colonies are beginning to flatten into epithelial-like cell sheets. The cells in the middle of the colony are AP negative and exhibit a flattened epithelial-like appearance. By contrast, cells in the perimeter are smaller, exhibit a multilayered morphology and possess cytoplasmic vesicles.- -